Point of view

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"Immune" functions of parenchymal cells might contribute to their susceptibility to rejection

John W. Fabre

Blond McIndoe Centre, Queen Victoria Hospital, East Grinstead, Sussex RH19 3DZ, UK

An intriguing phenomenon in transplantation has been the remarkable differences in susceptibility to rejection of transplants of different tissues. On the one hand, skin has always been noted to be particularly fiercely rejected [29] and long-term acceptance of skin grafts difficult to achieve. At the other end of the spectrum, liver allografts appear to be relatively privileged [5, 6, 14]. More recent work suggests that grafts of islets of Langerhans are rejected unusually strongly [31]. Several hypotheses have been proposed to explain these differences. Here, the older hypotheses are discussed and new proposals are put forward, based on recent findings which suggest that non-immune parenchymal cells contribute in various ways to the immune defences of the body. These "immune" functions of the parenchymal cells might contribute in a tissue-specific manner to their vulnerability to rejection.

The parenchymal cells of the body contribute to physiological immune responses in two ways: by secreting lymphokines (cytokines) such as interleukin-1 (IL-1) and by increasing their expression of class I and class II MHC antigens. Both of these properties vary markedly in different cell types, and it is proposed that this is the fundamental basis for the differential susceptibility to rejection of skin and liver grafts. A curious physiological vulnerability to over-expression of MHC antigens in insulin-secreting β-cells might contribute to the extreme vulnerability of islets of Langerhans to rejection.

Skin grafts behave in many curious ways when compared to organ grafts. For example, skin grafts are acutely rejected across minor histocompatibility barriers, which do not result in organ graft rejection, e.g. [10, 19, 32]. Moreover, protocols of immunosuppression which are highly effective for prolonging the survival of organ grafts have minimal effects on skin grafts [10]. A particularly interesting observation was that when recipient rats were subjected to three sequential grafts from the same donor strain in the order skin-skin-skin or skin-skin-kidney, the third skin grafts were rejected in a sensitised fashion while the kidney grafts survived longer than in untreated controls [10]. Finally, long-surviving recipients of kidney or heart allografts reject skin from the donor strain in normal [13, 16] or only slightly delayed fashion [20, 30] with minimal or no impairment of the function of the organ allograft.

Skin-specific transplantation antigens have usually been proposed to explain the greater vulnerability of skin grafts to rejection [25]. Although it is difficult to exclude this as an explanation, it is hard to imagine how one or even a few additional skin-specific minor histocompatibility antigens would make such a dramatic difference when added to the many dozens of more widely distributed minor histocompatibility antigens known to be involved in skin graft rejection [12]. Moreover, the survival of donor-strain skin grafts, placed on long-survivors of organ allografts, increases with the length of time the organ graft has been in place [22], and this argues for immunity to shared (presumably MHC) antigens being of primary importance. In contrast to organ grafts, skin is transplanted as a free graft to the body surface. However, direct vascularisation of skin grafts does not alter their behaviour [24]. Moreover, the location of skin grafts on the body surface seems also not to be of importance: pure keratinocyte grafts, placed under the renal capsule, are as vigorously rejected and their rejection is as difficult to suppress as that of conventional skin grafts [9].

The skin is the major barrier to invasion of the body by micro-organisms. It is therefore very interesting that keratinocytes have recently been shown to secrete IL-1 [17], IL-3 [7], and other poorly

defined T-cell-growth factors [8]. Clearly keratinocytes do not merely provide a passive physical barrier to invasion by micro-organisms, but play an active and major role in the body's defences. Lymphokine release by keratinocytes is likely to increase the strength of the immune response against invading pathogens and thereby to favour the survival of the host. However, when keratinocytes within grafted skin respond in this way, they very likely contribute to their own demise. Even weak immune responses against a skin graft are likely to be locally greatly augmented by the release of lymphokines by keratinocytes. The much greater strength of the rejection response against skin grafts, as well as their curious behaviour in various situations, as outlined in a preceding section, might well be explained by this phenomenon.

With liver allografts, a very interesting and early observation was that in some strains of pig liver allografts are not rejected, whereas kidney grafts are rapidly rejected [6]. This phenomenon is also seen in some rat strains [14], and rejection is said to be less of a problem in clinical liver grafting when compared with other organ grafts in man [5].

The release of soluble class-I MHC antigen by liver allografts has usually been proposed as the mechanism whereby this organ suppresses the immune response against itself [15]. It should be noted, however, that kidneys also contain [28] and secrete (S.C.Spencer, J.W.Fabre, in preparation) soluble class I MHC antigens. Moreover, large doses of soluble donor class-I MHC antigens did not influence the survival of rat heart allografts in the slightest [27].

The second way in which parenchymal cells contribute to the body's defences is by increasing their expression of MHC molecules. It is now well established that the physiological function of MHC molecules is the presentation of peptide fragments of foreign antigens to the T lymphocyte system [2, 4]. The increased expression of MHC antigens, induced by lymphokines and certain other stimuli, presumably increases the efficiency of antigen presentation. Within areas of inflammation resulting from viral and other infections, this response very likely augments the immune response against the pathogen and thereby favours survival of the host. However, within transplanted tissue, increased MHC expression is likely to increase the vulnerability of the graft to host effector mechanisms greatly and to be a potent driving force in the rejection process [11, 21, 23]. Once again, therefore, the graft contributes to its own destruction by responding to the inflammation of rejection in a manner normally favourable when the stimulus is a more physiological inflammation. Interestingly, however, the hepatocyte is remarkably resistant to class-II MHC induction. Even at the height of severe rejection episodes, and in contrast to skin, kidney and other grafts, the great majority of hepatocytes within a liver graft remain resolutely class II negative [26]. The physiological reason for this is not known. However, it might well contribute to the "privilege" of liver allografts.

Islets of Langerhans pose an interesting problem. A possible explanation for their susceptibility to rejection has come from very recent experiments with transgenic mice (i.e. mice which have had genes artificially added to their genome, usually by microinjection of DNA into the pronucleus of the fertilised egg). Transgenic mice which have high endogenous levels of isogenic class I or class II MHC antigens in the β-cells of their islets of Langerhans develop diabetes without any evidence of an immune response to the islets [1, 18]. This was an entirely unexpected result and suggests that high intracellular levels of MHC antigens are peculiarly toxic to the β-cells, perhaps because of the peptide binding capacity of the MHC molecules [3]. Given that the level of MHC expression during rejection may increase by 10-to-30-fold over resting levels, it seems possible that, in a β-cell, this could tilt the balance towards cell death. MHC induction could be a phenomenon of the rejection process, which is intrinsically toxic to the β-cell and thereby contributes to target cell death in a manner which might not operate in other tissues.

The concept of a concerted immune response by the parenchymal cells of the body and the immune system in the defence against infection is a new and intersting one. From the point of view of transplantation, it is particularly relevant that these parenchymal immune responses are likely to be deleterious when they are triggered in transplanted tissues. It is likely, therefore, that further developments in this area will be of fundamental importance to our improved understanding of the rejection response.

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